PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY	PCT
TO: FRANK B. DEHN & CO. 179 Queen victoria syrile 20 20 C C C C C C C C C C C C C C C C C	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION (PCT Rule 44.1)
	Cast of mailing (day/month/year) 13. 06. 2005
Applicant's or agent's file reference 61.81204/001	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB2004/002706	International filing date (day/month/year) 24/06/2004
Applicant ISIS INNOVATION LIMITED	
Where? Directly to the International Bursau of WIPO, 24 To Toneva 20, Switzerland, Fa For more detailed instructions, see the notes on the accordance. The applicant is hereby notified that no international search Article 17(2)(a) to that effect and the written opinion of the in With regard to the protest against payment of (an) addition the protest together with the decision thereon has been	in so of the Informational Application (see Rule 46): halfy 2 months from the date of transmittal of the details, see the notes on the accompanying sheet. chemin des Colombettes actimite No. (41–22) 740.14.35 mpanying sheet. report will be established and that the declaration under ternational Searching Authority are transmitted herewith. In transmitted to the International Bureau together with the test and the decision thereon to the designated Offices. Idicant will be notified as soon as a decision is made, einternational application will be published by the publication, a notice of withdrawal of the International ureau as provided in Fulles 90bis 1 and 90bis 3, respectively, all publication, a notice of withdrawal of the International surplication will be international Searching Authority to the such comments to all designated Offices unless an stablished. These comments would also be made available to fly date. The designated Offices, a demand for International preliminary withy into the national phase until 30 months from the priority of the provided of the provide

Name and mailing address of the International Searching Authority

Authorized officer Stefan Brell

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basio instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty, incase of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, also sell parts of the international application (claims, description and drawings) may be amended during the international principal self-international procedure, there is usually no need to file amendmental or the claims under Article 19 except where, e.g. the substitute of the purposes of provisional protection or has another reason for amending the claims before international protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittel of the international search report or 16 months from the priority date, whichever time limit expires later, it should be noted, however, that the amendments will be considered as harving been received on time if they are received by the International Bureau after the expiration of the applicable time Ilmit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the international Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required, in all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 200(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicent. However, it the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- the claim is unchanged;
- (ii) the claim is cancelled:
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding now claims;
 Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added.* or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the word. Statement under Article 19(1).

it may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article. 19, a domaind for international positioning years/ination has already been submitted, the applicant must pretently, at the same time of filing the amendments with the international Bureau, also file a copy of such amendments with the international Preliminary Examining Authority (see Rivel 62 (2.6), first extension).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be turnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicants or agents file reference FOR FURTHER See Form PCT/ISA/220					
1.81204/001 ACTION as well as, where applicable, item 5 below.					
International application No.	International filing date (day/month	/year) (Earliest) Priority Date (day/month/year)			
PCT/GB2004/002706 24/06/2004 24/06/2003					
Applicant					
ISIS INNOVATION LIMITED					
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Seam ansmitted to the International Bureau	ching Authority and is transmitted to the applicant			
This international Search Report consists	of a total of she	ets.			
X It is also accompanied by	a copy of each prior art document ci	ted in this report.			
Basis of the report With regard to the language, the language in which it was filed, unit	international search was carried out ess otherwise Indicated under this ite	on the basis of the international application in the			
The International this Authority (Rui	search was carried out on the basis (ie 23.1(b)).	of a translation of the International application furnished to			
b. With regard to any nucleo	otide and/or amino acid sequence	disclosed in the international application, see Box No. I.			
2. Certain claims were four	nd unsearchable (See Box II).				
3. X Unity of invention is lace	king (see Box Iii).				
4. With regard to the title,					
X the text is approved as su	bmitted by the applicant.				
the text has been establis	hed by this Authority to read as follow	vs:			
With regard to the abstract, The text is approved as su	A subtract to the contract of				
		is Authority as it appears in Box No. IV. The applicant			
may, within one month fro	m the date of mailing of this internati	onal search report, submit comments to this Authority.			
6. With regard to the drawings,					
a. the figure of the drawings to be p	ublished with the abstract is Figure I	No			
as suggested by t	• • • • • • • • • • • • • • • • • • • •				
	s Authority, because the applicant fa				
	s Authority, because this figure bette	r characterizes the invention.			
2. I note of the figures is to be	e published with the abstract.				

International Application No

PCT/GB2004/002706 A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H5/10 C12N9/56 C12N9/44 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) TPC 7 C07H C12N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data, BIOSIS C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X DATABASE CAPLUS 1-3.5.7. CHEMICAL ABSTRACTS SERVICE, COLUMBUS, 15.16 OHIO, US; XP002300619 retrieved from STN Database accession no. AN: 1955:53561 γ DN:49:53561, OREF:49:103061,10307a-e 1-5.7-9. abstract 11-13. 15-17 & YAMADA ET AL.: "Synthesis of thiamine alkyl disulfides" YAKUGAKU ZASSHI, no. 74. 1954, pages 963-966, -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. X ° Special categories of cited documents : "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the International *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another Yf document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-ments, such combination being obvious to a person skilled in the art. citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the International filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 13.06.2005 20 May 2005 Name and mailing address of the ISA Authorized officer

Steendijk, M

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International Application No PCT/GB2004/002706

ategory °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
~gory -	onation of occurrent, with indication, where appropriate, of the relevant passages	Helevant to claim No.
	FIELD ET AL.: "Biologically	1-3,7,
	orientated"	15,16
	J.ORG.CHEM.,	,
	vol. 36, no. 2, 1971, pages 309-313,	1
	XP002300617	1
'	page 309	1-5,7-9,
		11-13,
		15-17
	RAJCA A ET AL: "NEW MIXED DISULFIDES OF	1 5 7 15
	L-CYSTEINE DERIVATIVES AND OF GLUTATHIONE	1,5,7,15
	WITH DIETHYLDITHIOCARBAMIC ACID AND	
	2-MERCAPTOETHANESULFONIC ACID"	
	ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH,	1
	- EDITIO CANTOR. AULENDORF, DE.	
	vol. 40, no. 3, 1990, pages 282-286.	
	XP000882932	
	ISSN: 0004-4172	
	page 284	1-5,7-9,
		11-13,
		15-17
	RAJCA A ET AL: "SYNTHESIS OF	1-3,7,
	UNSYMMETRICAL DISULFIDES WITH	15,16
	THIOLSULFONATES IMMOBILISED ON A	10,10
	POLYSTYRENE SUPPORT"	1
	TETRAHEDRON LETTERS, ELSEVIER SCIENCE	
	PUBLISHERS, AMSTERDAM, NL,	
	vol. 31, no. 42, 1990, pages 6075-6076,	
	XP000653113	
	ISSN: 0040-4039	
	the whole document	1-5,7-9,
		11-13,
		15-17
	WO 00/01712 A (GENENCOR INT)	1-5,7-9,
	13 January 2000 (2000-01-13)	11-13,
	· (,	15-17
	page 6	
	JOHNSTON B D ET AL: "Synthesis of	
	thio-linked disaccharides by 1>2	8-10
	intramolecular thioglycosyl migration:	ŀ
	oxacarbenium versus episulfonium ion	l
	intermediates."	
	THE JOURNAL OF ORGANIC CHEMISTRY. 28 JUL	l
	2000,	1
	vol. 65, no. 15,	
	28 July 2000 (2000-07-28), pages	
	4607-4617, XP002328859	
	ISSN: 0022-3263	
	page 4611; compound 34	
	-/	
		1

International Application No PCT/GB2004/002706

	ntion) DOCUMENTS CONSIDERED TO BE RELEVANT	
tegory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	REICH H J ET AL: "ORGANOSELENIUM CHEMISTRY ALKYLATION OF ACID ESTER AMIDE AND KETONE ENOLATES WITH BROWOMETHYL BENZYL SELENIDE AND SULFIDE PREPARATION OF SELENOCYSTEINE DERIVATIVES" JOURNAL OF ORGANIC CHEMISTRY, vol. 51, no. 15, 1986, pages 2981–2988, XP002328860 ISSN: 0022-3263 p. 5551, scheme II	1,6,15
, ,χ	GAMBLIN DAVID P ET AL: "Glycosyl phenylthiosulfonates (glyco-PTS): novel reagents for glycoprotein synthesis." ORGANIC & BIOMOLECULAR CHEMISTRY. 7 NOV 2003, vol. 1, no. 21, 7 November 2003 (2003-11-07), pages 3642-3644, XP002300618 ISSN: 1477-0520 the whole document	1-5,7-9, 11-13, 15-17
Р,Х	GAMBLIN DAVID P ET AL: "Glyco-SeS: selenenyIsulfide-mediated protein glycoconjugation—a new strategy in post-translational modification." ANGEWANDE CHEMIE (INTERNATIONAL ED. IN ENGLISH) 6 FEB 2004, vol. 43, no. 7, 6 February 2004 (2004-02-06), pages 828-833, XP002328861 ISSN: 0570-0833 the whole document	1-6, 8-10, 14-29

International application No. PCT/GB2004/002706

INTERNATIONAL SEARCH REPORT

BOX II	Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This inter	rnational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
з. 🔲	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
This Inter	mational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1. X	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not Invite payment of any additional fee.
з. 🗌	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. 🔲	No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is estimated to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark o	on Protest The additional search fees were accompanied by the applicant's protest. X No protest accompanied the payment of additional search fees.

Information on patent family members

International Application No PCT/GB2004/002706

				10174	02001, 002.00
Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0001712	Α	13-01-2000	AU	749383 B2	27-06-2002
			ΑU	5208199 A	24-01-2000
			CA	2331783 A1	13-01-2000
			EP	1093459 A2	25-04-2001
			JP	2002519050 T	02-07-2002
			US	2002146803 A1	10-10-2002
			WO	0001712 A2	13-01-2000
			US	2001018200 A1	30-08-2001

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY PCT WRITTEN OPINION OF THE see form PCT/ISA/220 INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) Applicant's or agent's file reference FOR FURTHER ACTION see form PCT/ISA/220 See paragraph 2 below International application No. International filing date (day/month/year) Priority date (dav/month/year) PCT/GB2004/002706

24.06.2003

International Patent Classification (IPC) or both national classification and IPC C07H5/10, C12N9/56, C12N9/44

Applicant

ISIS INNOVATION LIMITED

 This opinion contains indication 	ons relating to the following items:
--	--------------------------------------

24.06.2004

Rox No I Basis of the opinion

Box No. II Priority

☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Box No. IV Lack of unity of invention

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Box No. VI Certain documents cited

☐ Box No. VII Certain defects in the international application

Box No. VIII Certain observations on the international application

FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority (IPEA'). However, this does not apply were the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/20

For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465

Authorized Officer

Telephone No. +49 89 2399-8460



_			
	Box	(No	o. I Basis of the opinion
1.	Wit the	h re lan	gard to the language , this opinion has been established on the basis of the international application in guage in which it was filed, unless otherwise indicated under this item.
		lar	is opinion has been established on the basis of a translation from the original language into the following guage , which is the language of a translation furnished for the purposes of international search ider Rules 12.3 and 23.1(b)).
2.	Wit	h re	gard to any nucleotide and/or amino acid sequence disclosed in the international application and ary to the claimed invention, this opinion has been established on the basis of:
	a. t	ype	of material:
	-	3	a sequence listing
	-		table(s) related to the sequence listing
	b. f	orm	at of material:
	- 1		in written format
	- 1		in computer readable form
	c. ti	me	of filing/furnishing:
	1		contained in the international application as filed.
	-		filed together with the international application in computer readable form.
	-		furnished subsequently to this Authority for the purposes of search.
3.		co	addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto s been flied or furnished, the required statements that the information in the subsequent or additional ples is identical to that in the application as filed or does not go beyond the application as filed, as propriate, were furnished.
4.	Add	ditio	nal comments:

Box No. VI Certain documents cited

 Certain published documents (Rules 43bis.1 and 70.10) and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

- The present application relates to methods and reagents for disulfide bond formation, in particular for glycosylating proteins using thiosulfonates which are not alkylthiosulfonates or selenylsulfides.
- 2) Cited documents:

D1: CAPLUS AN: 1955:53561

D2: J.ORG.CHEM., vol. 36, no. 2, 1971, pages 309-313,

D3: ARZN.FORSCH./DRUG RES., vol. 40, no. 3, 1990, pages 282-286

D4: TET. LETT., vol. 31, no. 42, 1990, pages 6075-6076.

D5: WO 00/01712 A

D6: J.ORG.CHEM., 2000, vol. 65, no. 15, pages 4607-4617

D7: J.ORG.CHEM., vol. 51, no. 15, 1986, pages 2981-2988,

D8: ORG.BIOMOL.CHEM., vol. 1, no. 21, (2003-11-07), pages 3642-3644

D9: ANG.CHEMIE (INT.), vol. 43, no. 7, (2004-02-06), pages 828-833.

The prirority of 24.6.03 seems valid for claims 1-17 and the priority of 12.12.03 seems valid for claims 18-29. Accordingly, D8 is only prior art with respect to claims 18-29, whereas D9 is not considered as prior art.

3) Novelty

3.1 Documents D1-D4 describe various thiosulfonates, including phenylthiosulfonates, for forming disulfide bonds with thiol-group comprising compounds, including aminoacid derivatives. In view of D1-D4 the subject-matter of claims 1-3,5,7,15 and 16 cannot be considered new.

These documents do not specifically describe the carbohydrate derivatives defined in claims 8-9,11-13 and 17 nor selenosulfide related compounds/reactions.

Document D6 describes a selenosulfide according to claims 8-10; this document does not, describe its application for preparing disulfide compounds nor its preparation as defined in present claim 14.

Document D7 describes the reaction of a selenosulfide with a thiol producing a disulfide, which is considered to anticipate the subject-matter of claims 1, 6 and 15.

3.2 Document D5 describes alkylthiosulfonates for forming disulfide bonds, in particular for glycosylating proteins, which is excluded from the present application.

Document D8 (only prior art for claims 18-29) describes the use of phenylthiosulfonates for preparing disulfide compounds without mention of selenosulfide compounds.

Document D9 describes selenosulfides in preparing disulfide compounds; this document is however not considered as prior art.

4) Inventive step

With respect to the new subject-matter document D5 may be considered as closest prior art. The problem to be solved may be seen in the provision of alternative agents for introducing disulfide linked groups, in particular carbohydrate-moieties. As solution the claimed matter would at present seem obvious to the person skilled in the art in view of D1-D4 (for thiosulfonates) and D7 (for selenosulfides) as these documents already describe various other thiosulfonates and selenosulfides as convenient reagents for the introduction of disulfide linked moieties.

With respect to claim 14 it is noted that document D6 may be considered as closest prior art. The alternative method for preparing this compound seems to reflect basic chemistry and would therefor prima facie not seem to involve an inventive step.

5) No unifying common distinguishing feature with respect to document D5, relating to related preparative methods, is evident between the subject-matter involving thiosulfonates on the one hand and selenosulfides on the other hand is evident. Furthermore, no common distinguishing feature with respect to D6 is evident amongst new selenosulfides and their application on the one hand and new methods for preparing (partly) known selenosulfides (claim 14) on the other hand.